Hereditary Cancer Syndromes: What the oncologist should know

Robin De Putter, MD
Onco-Genetics

National coordinator ERN GENTURIS

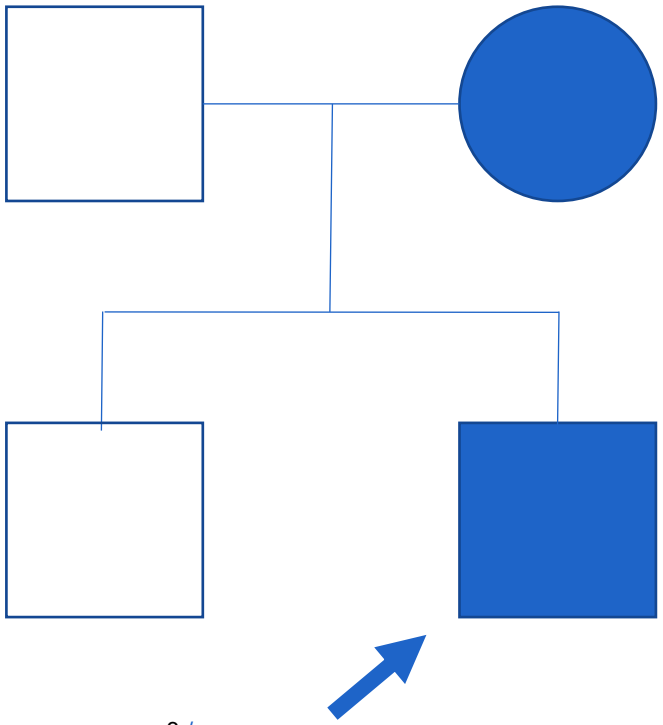
UZ GENT

UNIVERSITEIT GENT

Disclosures

- No conflict of interest

Case



Pheo 58 y

Paraganglioma 61 y

→ ~~SDHA VUS~~

→ VHL +

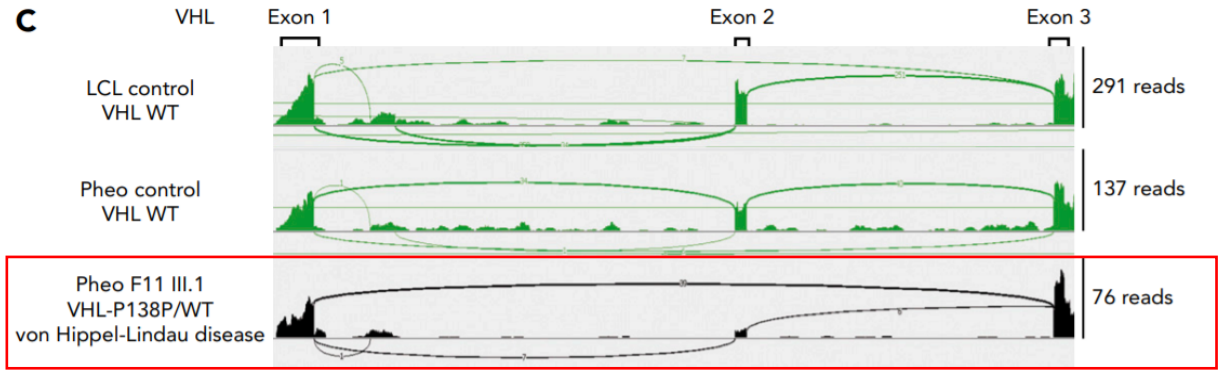
2018:

RED CELLS, IRON, AND ERYTHROPOIESIS

Identification of a new *VHL* exon and complex splicing alterations in familial erythrocytosis or von Hippel-Lindau disease

Marion Lenglet,[1-3,*] Florence Robriquet,[2,3,*] Klaus Schwarz,[4,5] Carme Camps,[6,7] Anne Couturier,[8] David Hoogewijs,[9] Alexandre Buffet,[10-12] Samantha J. L. Knight,[6,7] Sophie Gad,[1,13] Sophie Couvé,[1,13] Franck Chesnel,[8] Mathilde Pacault,[2,14] Pierre Lindenbaum,[3] Sylvie Job,[15] Solenne Dumont,[2] Thomas Besnard,[3,14] Marine Comec,[3] Helene Dreau,[16] Melissa Pentony,[6,7] Erika Kvikstad,[6,7] Sophie Deveaux,[17-20] Nelly Burnichon,[10-12,18,19,21] Sophie Ferlicot,[17,22] Mathias Vilaine,[2] Jean-Michaël Mazzella,[10-12,18,19,21] Fabrice Airaud,[14] Céline Garrec,[14] Laurence Heidet,[23] Sabine Irtan,[24] Elpis Mantadakis,[25] Karim Bouchireb,[23] Klaus-Michael Debatin,[26] Richard Redon,[3] Stéphane Bezieau,[3,14] Brigitte Bressac-de Paillerets,[13,27] Bin Tean Teh,[28] François Girodon,[29-31] Maria-Luigia Randi,[32] Maria Caterina Putti,[33] Vincent Bours,[34] Richard Van Wijk,[35] Joachim R. Göthert,[36] Antonis Kattamis,[37] Nicolas Janin,[38] Celeste Bento,[39] Jenny C. Taylor,[6,7] Yannick Arlot-Bonnemains,[8] Stéphane Richard,[1,13,17-20,†] Anne-Paule Gimenez-Roqueplo,[10-12,18,19,21,†] Holger Cario,[26,‡] and Betty Gardie[1-3,31,‡]

blood® 2 AUGUST 2018 | VOLUME 132, NUMBER 5



Pheochromocytoma 32 y → 2010: VHL, SDHD, SDHB and RET –

Contralateral pheo 37 y → 2015: ~~SDHA VUS (class 3)~~

pNET, RCC, hemangioblastoma 42 y → 2020: VHL c.414A>G; p.Pro138=

Normal result does NOT exclude a hereditary condition

- Techniques/knowledge may not allow detection of causal variant (false negative)
- Causal gene is not analysed or still unknown
- (Multifactorial inheritance)

→ **Risk estimation**

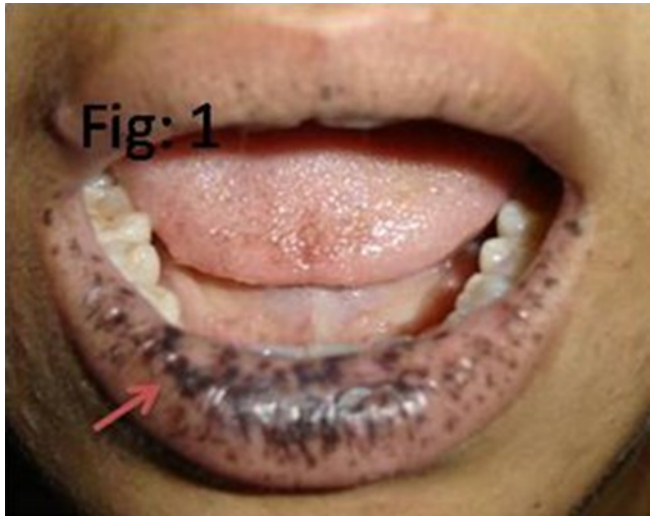
→ **Clinical criteria**

Clinical diagnostic criteria

- **A simplex case** (i.e., an individual with no known family history of **VHL** syndrome) presenting with **two or more** characteristic lesions:
  - Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
  - Renal cell carcinoma
  - Adrenal or extra-adrenal pheochromocytomas
  - Less commonly, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas
- **An individual with a family history of VHL syndrome** in whom one or more of the following syndrome manifestations is present:
  - Retinal angioma
  - Spinal or cerebellar hemangioblastoma
  - Adrenal or extra-adrenal pheochromocytoma
  - Renal cell carcinoma
  - Multiple renal and pancreatic cysts

Hereditary cause suspected?

- Young age at diagnoses
  → Earlier than “usual” age!
- Bilateral or multifocal
- Several *associated* cancers in one individual
- Strong family history
- Specific clinical features (rare)
- **Rare tumors**
- **Somatic mutations in predisposition genes?**



Rare tumors with high probability of germline predisposition

Ovarian Cancer	*BRCA1/2, …*
Pancreatic adenocarcinoma	*BRCA1/2, …*
Adrenocortical carcinoma	*TP53*
Thymic gland carcinoid tumors	*MEN1*
Medullary thyroid cancer	MEN2 (*RET*)
Pheochromocytoma / paraganglioma	MEN2, *SDHx, VHL*, …
Sex cord tumors with annular tubules	Peutz-Jeghers (*STK11*)
Large-cell calcifying Sertoli cell tumors of the testes	*STK11,* Carney (*PRKAR1A*)
MPNST	*NF1*
Acoustic or vestibular Schwannomas	*NF2*
Choroid plexus carcinoma	*TP53*
Hemagioblastoma	*VHL*
Chromophobe oncocytotic and/or hybrid renal tumors	Birt-Hogg-Dubé (*FLCN*)
Endolymphatic sac tumour	*VHL*
Sebaceous carcinoma	Lynch / Muir-Torre
Multiple cutaneous leiomyomas	HLRCC (FH)
Desmoid tumor	FAP (*APC)*
Pulmonary pleuroblastoma	*DICER1*
Jaw osteosarcoma	*TP53*

Adapted from: Banks KC, Moline JJ, Marvin ML, Newlin AC, Vogel KJ. 10 rare tumors that warrant a genetics referral. Fam Cancer. 2013 Mar;12(1):1-18. doi: 10.1007/s10689-012-9584-9. PMID: 23377869.

Tumor sequencing: somatic vs germline?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1221–1231, 2019
doi:10.1093/annonc/mdz136
Published online 3 May 2019

SPECIAL ARTICLE

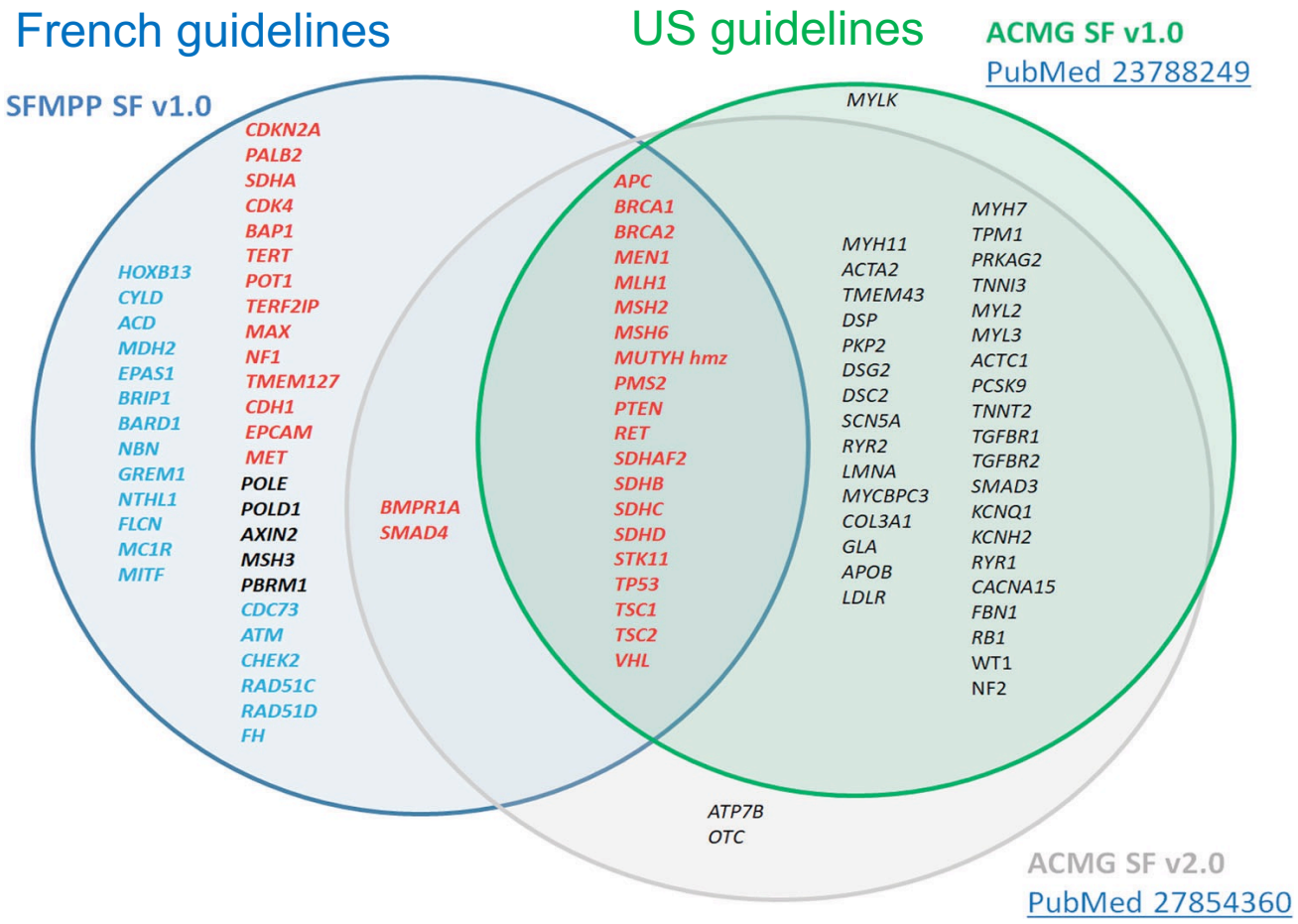
Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group

D. Mandelker[1*], M. Donoghue[2], S. Talukdar[3], C. Bandlamudi[2], P. Srinivasan[2], M. Vivek[4,5], S. Jezdic[6], H. Hanson[3], K. Snape[3], A. Kulkarni[7], L. Hawkes[8], J.-Y. Douillard[6], S. E. Wallace[9], E. Rial-Sebbag[10], F. Meric-Bersntam[11], A. George[12,13], D. Chubb[13], C. Loveday[13], M. Ladanyi[1,4], M. F. Berger[1,2], B. S. Taylor[2,3,5] & C. Turnbull[7,13,14,15*]

- 16 322 paired samples (tumor + germline)

→ 1494 (8.7%) germline mutations in 65 CPS genes

Germline actionable genes often found in tumor panels



Group 1
- Screening and/or prevention strategies available
- Follow-up germline testing recommended

Group 2
- Genes with significant risks
- Detection/prevention possibilities but level of evidence too low to measure the real benefit of an intervention in asymptomatic setting (not yet sufficient evidence to develop guidelines)

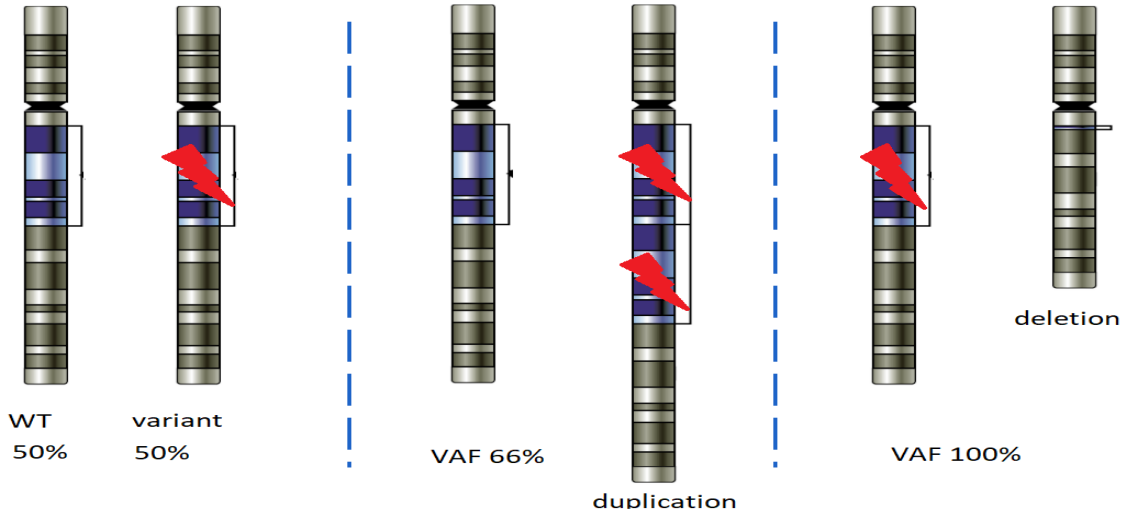
Group 3
- Genes with moderate risk of cancer and/or prevention
- Limited or nonexistent therapeutic possibilities
- Not recommended to give information to the patients

Pujol et al. Eur J Hum Genet. 2018 Dec;26(12):1732-1742

VAF in tumor material ↔ germline origin?

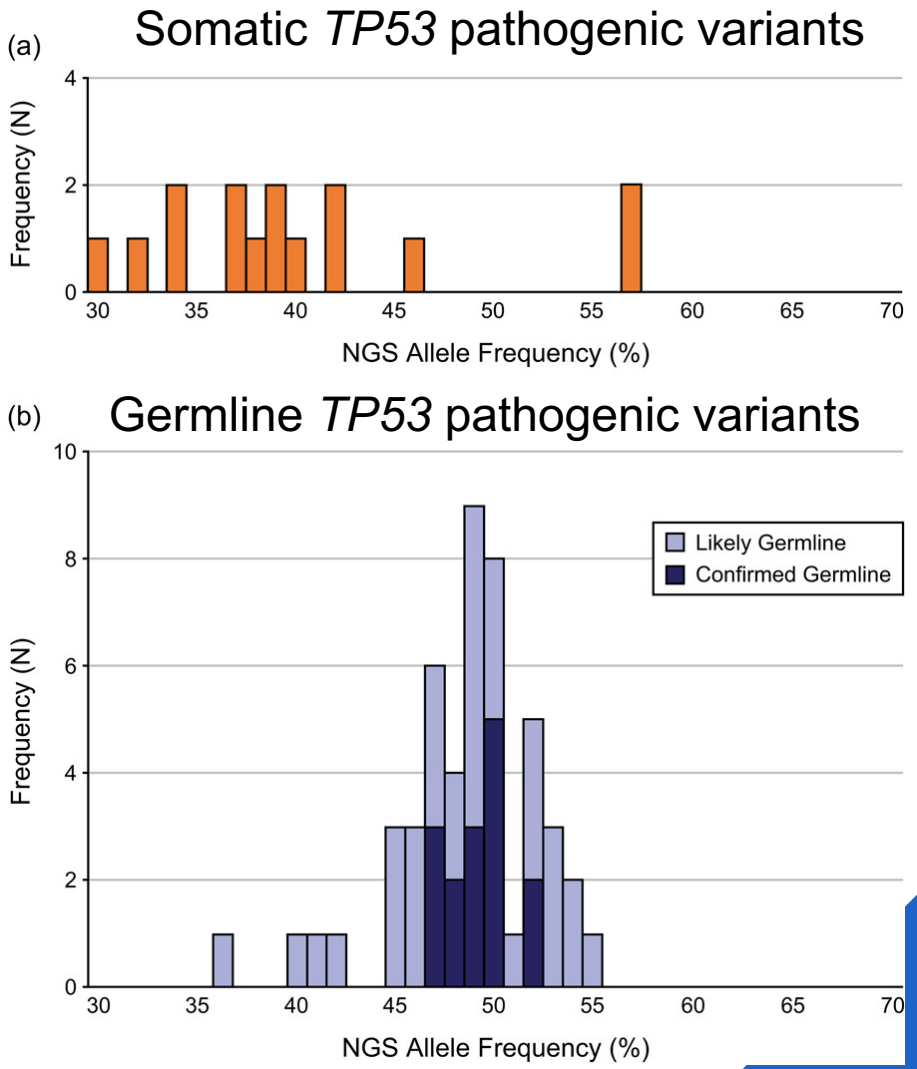
General rule:

Theoretically: heterozygous variant VAF=50% (30-70%)



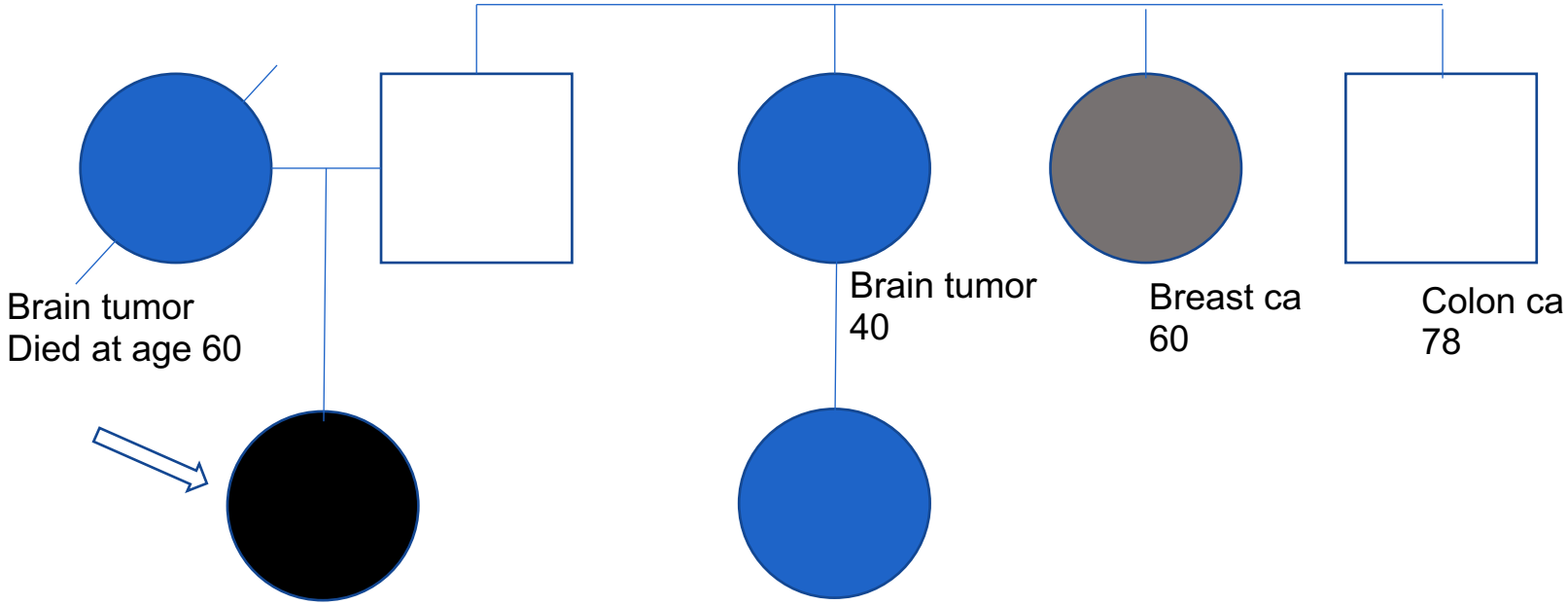
BUT - VAF affected by

- tissue heterogeneity
- tumor / clonal heterogeneity
- copy number abnormalities
- sequencing artifacts, statistical fluctuation particularly with shallow sequencing depths



COFFEE ET AL, HUMAN MUTATION 2019

Case example (1)



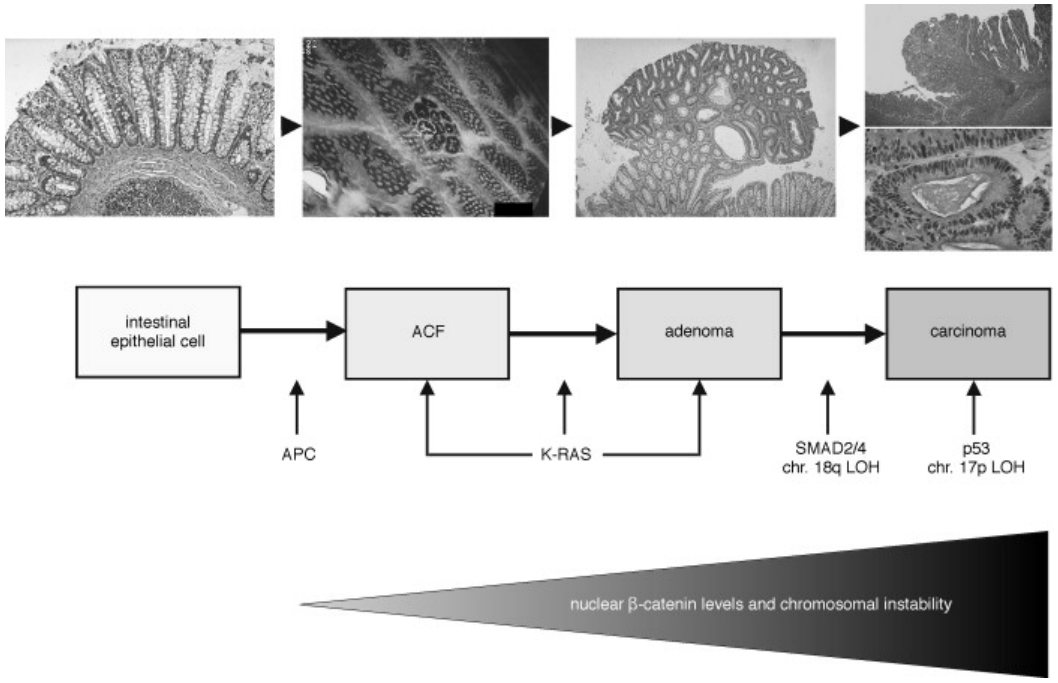
Solid tumor NGS panel on cholangiocarcinoma (60% tumor cells):

- CDKN2A c.266_275delinsAAG p.(Gly89GlufsTer55) (VAF=71%)
- TP53 c.848G>C p.(Arg283Pro) (VAF=88%)
- Deletion PTEN

EDTA blood: none of the variants detected

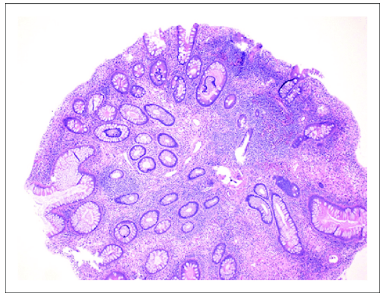
Tumor mutation spectrum

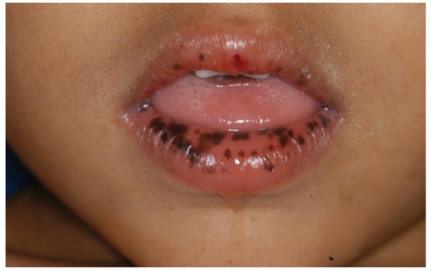
APC



STK11

- Somatic STK11: lung ca, rare in CRC (1%)
- Germline:
  - Peutz-Jeghers syndrome (STK11):
    - Increased risk for a wide variety of epithelial malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers)
    - Mucocutaneous pigmentation





Mansoor et al. International Journal of Surgical Pathology 2013

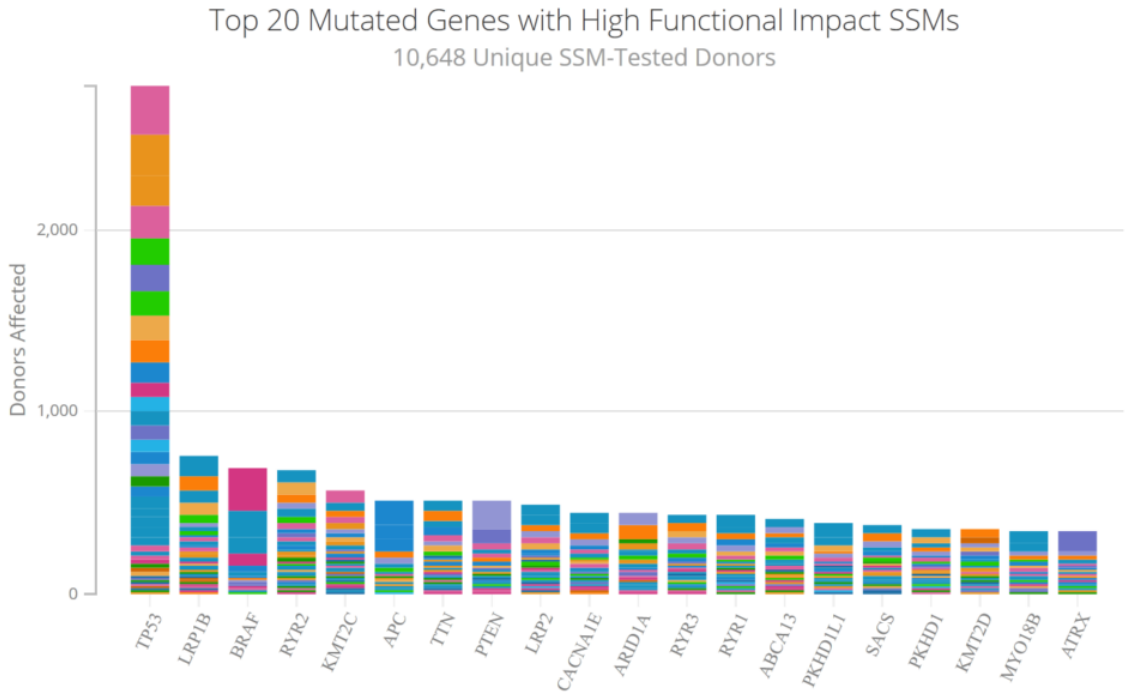
Tumor mutation spectrum*: TP53* - Li Fraumeni

- High prevalence of somatic mutations in cancer
- <1% germline
- +/- 6,8 % if diagnosed <30y
- >10% in associated tumors <30y (non CNS)

Table 3. 2015 Version of Chompret Criteria

Familial presentation	Proband with tumor belonging to LFS tumor spectrum (eg, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 yr, AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 yr or with multiple tumors
Multiple primitive tumors	Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 yr
Rare tumors	Patient with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history
Early-onset breast cancer	Breast cancer before age 31 yr

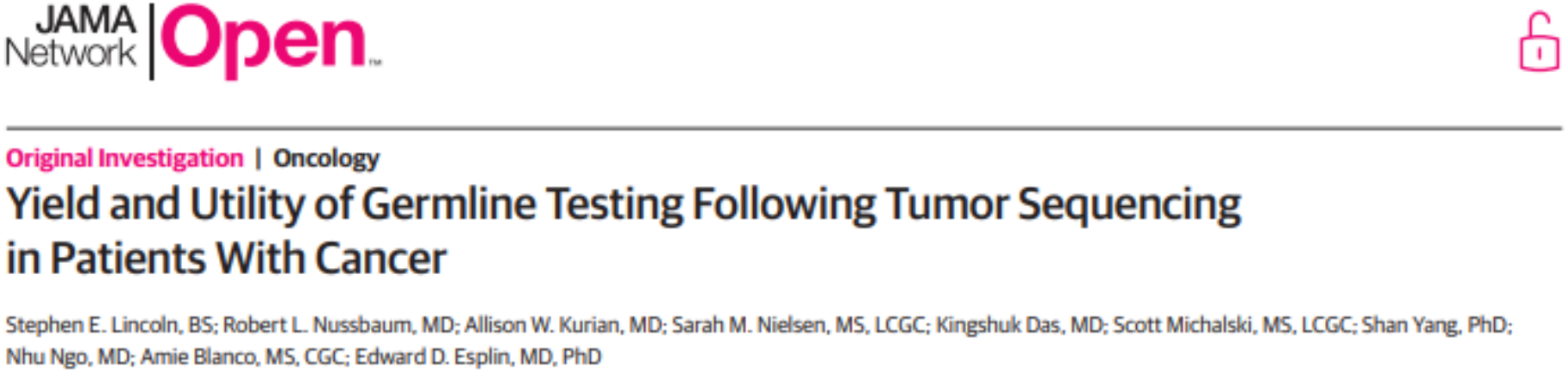
Abbreviation: LFS, Li-Fraumeni syndrome.



Considerations to determine if referral for germline testing is warranted

- Known cancer predispositions gene:
  - Most frequent : ATM, BRCA1, BRCA2, CHEK2, DDX41, GATA2, …
- VAF > 30 %
- Normal tumor mutation spectrum
- Founder mutations
- Same variant in multiple primary tumors of the same individual
- Hypermutated tumors
- Personal and family history consistent with affected gene / phenotype

Is tumor sequencing is sufficient to rule out a germline variant?



JAMA Network | Open

Original Investigation | Oncology

Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer

Stephen E. Lincoln, BS; Robert L. Nussbaum, MD; Allison W. Kurian, MD; Sarah M. Nielsen, MS, LCGC; Kingshuk Das, MD; Scott Michalski, MS, LCGC; Shan Yang, PhD; Nhu Ngo, MD; Amie Blanco, MS, CGC; Edward D. Esplin, MD, PhD

- 2023 cancer patients
- Pathogenic germline variants in 617 (30.5%)
- **8.1% of germline mutations were missed by tumor sequencing**

Take home messages

- A germline VUS should not be used for clinical descisions
- Bilateral, multifocal and rare tumors are more likely to be hereditary
- Normal results ≠ normal risk / sporadic
  → familial risk (SNPs/environment), wrong technique/gene, non-coding variants
- Substantial burden of germline variants across a range of tumor histologies
  → Preferably inform the patient prior to genetic tumor testing about potentially revealing data with clinical impact for relatives
- Consider referral for genetic counseling in somatic variants with suspicion of germline origin
  → High VAF (>30%) in an actionable cancer predisposition gene, …
- Tumor testing cannot substitute for germline testing